As the limits of surgical therapy have been extended to include more extensive procedures in the elderly and the critically ill, it has become increasingly apparent that adequate care of such patients demands that the surgeon and the anesthesiologist obtain an estimate of myocardial capacity. This evaluation should enable prediction of borderline myocardial contractility prior to the onset of cardiac decompensation, so that prophylactic measures may be instituted. The usual clinical characterization is not entirely satisfactory, since circulatory congestion is nonspecific, and may be present in instances where the heart does not fail as a muscle; conversely, and more important, the heart may be a failing muscle and yet not manifest failure as a pump in the absence of stress.

In the past decade it has become clear that myocardial contraction can be classified in terms of the force-velocity relationship originally derived from observations of contraction of skeletal muscle. However, in contrast to skeletal muscle, in which there is only a single mechanism for increasing strength of contraction, in cardiac muscle there are two mechanisms by which myocardial force may be increased: the classic Frank-Starling mechanism, by which increments in the resting length of the muscle fiber prior to contraction increase developed force; and an isotropic mechanism, by which alteration in the rate of activation or in the biochemical environment of the cardiac muscle fiber can increase developed force at a constant resting fiber length. A thorough understanding of the fundamental difference between these two mechanisms of myocardial contraction is essential not only for quantification of myocardial contractility, but also for the rational use of therapeutic measures to alter the myocardial contractile state.

The Mechanics of Myocardial Contraction

A view of the mechanics of myocardial contraction is largely derived from the monumental studies of the frog sartorius muscle by A. V. Hill and his disciples. These concepts have been extended to an analysis of the mechanical activity of cardiac muscle by Abbott and Mommaerts and Sonnenblick and they provide a useful conceptual model which enables explanation of the events of contraction both in isolated cardiac muscle and in the intact heart. In this model, a contractile element (CE) is arranged in series with a passive elastic element (SE). The contractile element is thought to be freely extensible at rest, but is capable of force development or shortening during activation. The series elastic component (SE) is also thought to bear negligible tension at rest, but is stretched during the activation and contraction of the contractile element. A second passive elastic component is arranged in parallel (PE) with the contractile unit (CE) and the series elastic element (SE). This passive elastic element is thought to bear the resting tension and to be responsible for the myocardial diastolic pressure-volume relationship. There are probably viscous factors as well, but these do not appear important in the normal operation of cardiac muscle.

With this model in mind, it becomes pos-
sible to explain the mechanism of contraction of cardiac muscle under isometric conditions, where no external shortening is permitted, and under isotonic conditions, where the muscle is allowed to shorten externally during contraction. In the former case (fig. 1), following activation, the contractile element (CE) shortens, stretching the series elastic component and at the same time producing external force proportional to the state of the contractile element and the stress-strain properties of the series elastic element. In isotonic contraction the cardiac muscle fiber, at a given resting length determined by the preload or diastolic volume in the heart, is permitted to shorten while lifting an afterload. Following activation, the contractile element (CE) shortens in a manner similar to that described for the isotonic contraction (fig. 1), stretching the series elastic element (SE) until the force generated becomes equal to the afterload. When the force is equal to the load, the entire muscle will shorten and lift the afterload at a rate and to a distance proportional to the properties of the contractile element. Once the shortening occurs, the force stretching the series elastic element (SE) remains constant, and the time course of shortening of the complete system reflects only the shortening properties of the contractile element. This force-velocity relationship characterizes the contractile state of both skeletal muscle and myocardium. The unique property of myocardial muscle which distinguishes it from skeletal muscle is that, under ordinary circumstances, it operates as a cyclic engine. During each cycle the duration of activation of the contractile element is reflected in the duration of myocardial contraction. The mechanical consequences resulting from this active state reflect the intensity, rate, and duration of the mechanochemical process in the contractile element which generates both the force and the velocity properties of the myocardial fiber. At any given fiber length the series elastic component (SE) is unaltered by interventions which change the active state of the contractile element (CE). Therefore, the velocity and acceleration of isometric force development in the myocardium reflect only the characteristics of the contractile element.

Under ordinary circumstances, the myocardial fibers in the intact heart both generate tension during isovolumetric contraction and shorten during systolic ejection. The interaction between these aspects of contraction can be demonstrated clearly in the experimental system provided by the isolated papillary muscle. When the papillary muscle, held at a constant resting length, is permitted to contract against increasing afterload increments (fig. 2), it contracts isometrically until the tension which it generates equals the afterload, and then the muscle shortens. This is similar to the circumstances of myocardial contraction made from isolated papillary muscle held in such a manner that both initial isometric contraction and subsequent isotonic shortening are possible. Below: serial isometric contraction at increasing afterloads (horizontal lines). Above: successive isotonic shortening corresponding to the increasing afterloads in the lower tracing (dotted lines). (From Siegel et al., with permission of the publisher.)
traction occurring in the intact heart, where the left ventricle contracts isovolumetrically until the intraventricular pressure generated equals the aortic diastolic pressure, and ejection with shortening of the myocardial muscle occurs. This series of overlay tracings shows that when the afterload is very small there is essentially no period of tension development and the muscle shortens maximally at a maximum velocity. As the afterload is increased there is a progressive increase in the isometric tension developed prior to shortening, but muscle shortening and the velocity of shortening are both decreased as the afterload becomes greater. When the afterload is equal to or greater than the maximum force which can be generated by the contractile element, a totally isometric contraction occurs and there is no external shortening. In the intact heart at any given length or diastolic volume, this is roughly equivalent to increasing the level of aortic diastolic pressure.

In this kind of preparation, it is possible to compare the relationships between velocity of myocardial shortening, myocardial work, and velocity of isometric force development as functions of the afterload imposed on the isotonically contracting muscle. The change in velocity of isotonic shortening at a constant initial fiber length, occurring as increasing afterloads are lifted, is the classic force-velocity relation. This relationship, shown in the upper panel of figure 3, describes the contractile process under given conditions. The point at which the force-velocity relation meets the load axis corresponds to the maximum isometric force (P₀) generated by the contracting muscle. The point at which the extrapolated curve crosses the velocity axis is the maximum velocity of shortening of the contractile element (Vₘₐₓ) of the unloaded muscle. This curve describes a single level of contractility, at a given fiber length.

In the middle panel (fig. 3) isotonic shortening of the papillary muscle is plotted against increasing afterload, demonstrating that with an increasing load shortening, like the velocity of shortening, decreases. In this panel also, myocardial work is plotted as a function of the increasing load. At a single fiber length and constant biochemical environment and heart rate, the work-load relationship is a hyperbolic curve intercepting the load axis at zero load and at isometricity. Myocardial power is developed force times velocity of shortening and, therefore, a similar relation exists for this function. Since each force-velocity relationship describes a single state of the contractile element of the myocardium, it is obvious that, in the presence of changing afterload, beat work or power cannot be used as an absolute index of contractility.

The second feature important in understanding the nature of myocardial contraction is that, as long as initial fiber length is held constant prior to shortening, the time course of isometric tension development (dp/dt) up to the time at which shortening occurs is identical to that inscribed by the completely isometric muscle at the same initial fiber length (fig. 2).
In both isolated papillary muscle (fig. 3, lower panel) and intact heart, when the instantaneous value of $dp/dt$ immediately prior to shortening (or ejection) was determined as a function of the afterload, maximum $dp/dt$ occurred at $36 \pm 6$ percent of the peak isometric load. Similar data were found over a wide range of stimulation frequencies and in the presence of physiologic alterations in chemical inotropic backgrounds. In the absence of valvular insufficiency or abnormal vasoconstriction, studies in the intact ejecting heart suggest that valve opening occurs between 30 and 50 percent of the peak isometric pressure which the ventricle can achieve at that fiber length.

**The Frank-Starling Mechanism**

On the basis of the force-velocity relationship it is possible to describe rigorously the two basic mechanisms by which the myocardium may alter the characteristics of its contraction. Under the Frank-Starling mechanism, when a resting myocardial fiber obtained from the papillary muscle is stretched, or the intact ventricle is dilated by increments in diastolic volume, there occurs an increase in the resting tension (end-diastolic pressure) and in the developed tension with the succeeding contraction, up to a peak developed tension (fig. 4A). With continuing extension at rest there is no further increase in developed tension, although total tension increases due to an elevation of resting tension. If extension of the resting myocardial fibers continues, as with further diastolic dilatation of the heart, the developed tension decreases. If, however, at each point on this isometric length-tension curve, one permits the myocardial muscle fiber to contract isotonically against an increasing afterload, and examines the qualitative aspects of the alteration in the force-velocity relationship which underlies the operation of the Frank-Starling mechanism, it can be seen that...
Fig. 5. Papillary muscle, demonstrating the interrelationship between the force-velocity curve (A panels), the course of development (B panels), and the myocardial work (C panels) under conditions of varying fiber length. Changing stimulation frequency 2, and after administration of propranolol (C panels) are shown in the box above each A panel. (From Siegel et al., with permission of the publisher.)
changes in the force-velocity relationship characteristic of increasing length (Fig. 5, 1A) are characterized by an increase in the peak isometric force ($P_0$) without change in the maximum velocity of isotonic shortening ($V_{max}$). This constant maximum velocity of contractile element shortening has been theorized to represent the fundamental aspect of the Frank-Starling relationship.

This constancy in the $V_{max}$ of isotonic contraction has its parallel in the dynamics of isometric contraction. When one examines superimposed tracings of successive contractions of an isometric papillary muscle (Fig. 6), it can also be seen that at constant stimulation rate, increments in resting fiber length alone produce no alteration in the duration of the systolic phase of isometric contraction, from onset to peak tension. Similarly, volume changes in the isometric ventricle, like length changes in the isometric papillary muscle, produce no alterations in time to peak pressure.

Increases in the initial length of the resting myocardial fiber, while producing increases in both resting and developed tensions, also produce increases in the maximum rate of development of isometric tension ($dp/dt$) (Fig. 6). These are accompanied by parallel increases in the integrated systolic isometric tension (IIT) occurring from the onset of contraction to peak systole, or any fraction thereof. This IIT constitutes the impulse force generated by the isometrically contracting fiber. Under isotonic conditions this force impels the ejected volume from the intact heart. At a given frequency of stimulation, both the impulsive force (IIT) and the maximum rate of its development ($dp/dt$) increase in a parallel fashion with increases in end-diastolic volume or fiber length (Fig. 4C). The plateau and then decline of developed tension associated with excessive extension (Fig. 4A) is also associated with a plateau and then decline in both IIT and dp/dt (Fig. 4C). However, the ratio $dp/dt / IIT$ remains constant over the entire range of extension (Fig. 4B). As Figure 4C shows, the points on both ascending and descending limbs of the length-tension relationships fall upon the same line, which extrapolates through zero. The slope of this line reflects the duration of contraction. A single point in this isometric time-tension relationship, therefore, characterizes the entire length-tension relationship, and reflects the constancy of $V_{max}$ under the Frank-Starling mechanism. From this it has been implied that another characteristic of the Frank-Starling relationship is that even though the intensity of the active state generated by the contractile element is increased with increasing fiber length (as evidenced by increases in both the impulsive force generated and the rate of this force development), the duration of active state remains unchanged and reflects the constancy of the $V_{max}$ at a constant contractile state.

Examination of the isometric and isotonic aspects of myocardial contraction simultaneously (Fig. 5, 1A & B), discloses that for a given set of force-velocity curves with the same $V_{max}$, the maximum rate of isometric force development ($dp/dt$) occurs at approximately a third of the peak load regardless of the length. As noted for the time to peak isometric systole, the time from the activating stimulus to the maximum $dp/dt$ ($\Delta t dp/dt$) (Fig. 5, 1A) is also a constant for a given Frank-Starling relation with a constant $V_{max}$ and a manifestation of a constant duration of active state in the contractile element.
dp/dt has also been unaltered by changes in diastolic volume in the isovolumetric ventricle and by changes in end-diastolic pressure in the intact ejecting hearts of dog and man,\textsuperscript{166} provided that the minimum level of valve opening is at least 35 per cent of the potential isometric force so that the maximum dp/dt is truly achieved.

The hyperbolic curves inscribed by the external work (fig. 5, 1C) at different fiber lengths with the same \( V_{\text{max}} \) are such that increasing fiber length causes increases in both maximum work and the load at which this work is performed. In general, there is a tendency for the intact heart to operate at or near its maximum-work point.\textsuperscript{186, 153}

Thus, the constancy of \( V_{\text{max}} \) with increasing length in the force-velocity relationship, the characteristic feature of the Frank-Starling mechanism, is reflected empirically in the isometric contraction by a constant \( \Delta t \) dp/dt.

This is a manifestation of a constant acceleration of myocardial force. These characteristics, rather than any given work-length relationship, are the constants which quantitatively define a unique state of contractility.

**THE INOTROPIC MECHANISM**

The second basic mechanism of operation enables the myocardium to achieve increases in developed force and rate of force generation without an increase in resting fiber length. This inotropic mechanism involves an increase in the fundamental rate of the mechanochemical transformation in the contractile element and is characterized by an increase in the maximum velocity of isotonic shortening (\( V_{\text{max}} \)).\textsuperscript{1, 156, 157, 159} The inotropic mechanism can be invoked either by increases in the rate of myocardial contractile element activation\textsuperscript{1, 140, 112, 186} or by changing the biochemical environment of the cardiac muscle fiber.\textsuperscript{7, 156}

![Diagram A: Papillary Muscle](image1)

**Fig. 7.** Comparison of the effects of calcium and norepinephrine on myocardial time-tension relations. **Ordinate:** Maximum rate of development of isometric tension (dp/dt). **Abscissa:** Integrated systolic isometric tension (IIT). A. Papillary muscle, initial length 9 mm, cross section 0.8 mm, T 23° C. From left to right, each group of three points (Control, Ca, NE) represents a single fiber length. Initial fiber length increased by 0.5 mm between groups of points. \( \frac{dp/dt}{IIT} \): control = 25.0; Ca (5.0 mM/l) = 30.0; NE = 45.0. B. Isometric ventricle. From left to right, each control value represents a 1-ml volume increment over an initial 12-ml volume. The first and fifth points are controls for the first and second stellate points, respectively. The second, third, and fourth points are controls for the first, second, third, and fourth calcium points, respectively. \( \frac{dp/dt}{IIT} \): control = 175; Ca = 236; stellate = 294. (From Siegel and Sonnenblick,\textsuperscript{119} with permission of the publisher.)
The changes in force-velocity relationships induced by increasing the rate of myocardial activation (or heart rate) at a constant length are shown in figure 5, 2A. The peak isometric force (maximum load) may increase slightly. However, the maximum velocity of shortening ($V_{\text{max}}$) is markedly increased. The maximum $dp/dt$ also occurs at about a third of the peak isometric load (fig. 5, 2B); however, the higher the activation rate, the higher the value of $dp/dt$ at any given load. The time from the activating stimulus to maximum $dp/dt$ ($\Delta t$ $dp/dt$) is decreased as the stimulation rate is increased (fig. 5, 2A). This decrease is proportional to the decrease in time to peak isometric force, and is also independent of fiber length.\textsuperscript{178, 180} External work is little altered by increasing the stimulation rate (fig. 5, 2C). At higher frequencies, no change in work occurs despite an increase in the maximum velocity of shortening and in $dp/dt$.\textsuperscript{180, 186} However, regardless of work or tension levels, increases in $V_{\text{max}}$ produced by increasing stimulation frequency are always associated with decreases in $\Delta t$ $dp/dt$.\textsuperscript{150, 180} and therefore represent an increased acceleration of myocardial force.\textsuperscript{178, 180, 216}

Following addition of a chemical positive inotropic agent (e.g., norepinephrine) at constant length and activation rate (fig. 5, 3A), the force-velocity relationship is altered in that both the peak isometric force ($P_o$) and maximum velocity of shortening ($V_{\text{max}}$) are increased.\textsuperscript{1, 166} As with rate increases, maximum $dp/dt$ is achieved at about a third of the peak isometric force level, and the value for $dp/dt$ is higher at any given load (fig. 5, 3B). The $\Delta t$ $dp/dt$ decreases to a new constant value proportional to the decrease in time to peak isometric force, and is also independent of the fiber length (fig. 5, 3A). Maximum external work and the load at which this work is achieved are both increased (fig. 5, 3C). Here also, the decrease in $\Delta t$ $dp/dt$ and the increase in acceleration of myocardial force are related to the increment in $V_{\text{max}}$.\textsuperscript{180} The latter effect of positive inotropic agents is the consequence of a decrease in duration of the active state.\textsuperscript{180} and is reflected in the shift to a steeper slope of the relationship between the rate of development of isometric force ($dp/dt$) and the impulsive force generated (IIIT) (fig. 7).\textsuperscript{178, 180} All chemical positive inotropic agents which have been studied decrease the duration of active state, although with some (calcium, digitalis, glucagon), the magnitude of this decrease may be small.\textsuperscript{21, 75, 190}

Chemical positive inotropic agents can also increase the intensity of the active state generated from a given fiber length. This is reflected by an increase in $dp/dt$ and the total isometric force developed from a given fiber length. All of the positive inotropic interventions which have been studied, norepinephrine,\textsuperscript{1, 27, 76, 118, 123, 175, 185, 186} isoproterenol,\textsuperscript{75, 95, 171} calcium,\textsuperscript{175, 186, 187} digitalis,\textsuperscript{14, 15, 124, 125, 170, 190} glucagon,\textsuperscript{75, 110} angiotensin,\textsuperscript{24, 181} and sustained post-extrasystolic potentiation (paired pacing)\textsuperscript{17} increase the maximum velocity ($V_{\text{max}}$) of the force-velocity relation, the intensity of active state, and the force of isometric contraction.

Chemical negative inotropic intervention, such as pentobarbital, decrease $V_{\text{max}}$ and the intensity of active state. They also increase the duration of active state.\textsuperscript{182, 179} These effects result in a decrease in the developed force occurring at a given fiber length.\textsuperscript{5, 78, 143, 179} Similar increases in the duration of active state, reflected in the increase in $\Delta t$ $dp/dt$, follow administration of E. coli endotoxin to intact animals; \textit{in vitro} this agent also appears to qualify as a negative biochemical inotropic agent.\textsuperscript{171} There is some evidence that halothane\textsuperscript{50, 207} and methoxyflurane\textsuperscript{163, 206} can dissociate alterations in $V_{\text{max}}$ from changes in duration of active state. Both produce decreases in $V_{\text{max}}$.\textsuperscript{163, 207} and in the intensity of active state (peak tension).\textsuperscript{11, 131, 183} but the increase $\Delta t$ $dp/dt$ occurs only at high concentrations of halothane,\textsuperscript{207} and this may actually decrease during methoxyflurane.\textsuperscript{206} The latter may have special significance since methoxyflurane has been reported to prevent an increase in $V_{\text{max}}$ during concomitant norepinephrine administration, while permitting increases in $P_o$ to occur.\textsuperscript{184} In any event, this phenomenon demands further study in relation to the associated abnormalities in myocardial energy metabolism. Among other anesthetic agents, diethyl ether,\textsuperscript{19, 113, 116, 143} cyclopropane,\textsuperscript{116, 143, 144} and CI-581 \textsuperscript{22} have been re-
ported to decrease myocardial contractile force from a constant fiber length, but the details of their specific actions on myocardial force–velocity and isometric time–tension relations have only been speculated. Nitrous oxide has no effect on the rate of development of isometric tension (dp/dt) at constant fiber length, and presumably has no direct effect on myocardial force–velocity relationships.

In summary, a change in the maximum velocity of the contractile process (V_{\text{max}}), and the associated alteration in duration of the active state serve to define and to quantify a given inotropic or contractile state of the myocardium. Operation under the inotropic mechanism results in an alteration of the acceleration of isometric myocardial force \( \frac{dp}{dt} \). Increases in fiber length which represent the Frank–Starling mechanism are characterized by increases in intensity of the active state and force developed during isometric contraction, but fiber length changes are not associated with changes in either V_{\text{max}} or alterations in the duration of the active state, and they involve no change in the acceleration of myocardial force \( \frac{dp}{dt} \). Thus, alteration in the velocity-dependent aspects of the force–velocity relationship and in the duration of the active state are the fundamental differences between the inotropic mechanism, involving a true change in myocardial contractility, and the Frank–Starling mechanism, which does not involve a change in contractility.

**The Ultrastructural Basis for Myocardial Contractility**

Although very little is known about the intrinsic subcellular process by which inotropic effects are brought about, the basis for the Frank–Starling mechanism is unquestionably ultrastructural. The basic ultrastructural unit, which provides the mechancial model for myocardial contraction, is the myocardial sarcomere. While it is beyond the scope of this review to consider the biochemical mechanisms involved in the contractile process, it is conceptually useful to consider briefly the organization of this basic contractile unit. Careful studies by x-ray diffraction techniques and electron microscopy in both cardiac and skeletal muscle suggest that the contractile element of a sarcomere is composed of partially overlapping, rod-like filaments of two types:
thick filaments, composed of the protein myosin (myosin A), about 100\(\lambda\) in diameter and 1.5 to 1.6 microns in length; and thin filaments composed primarily of actin which are approximately 50\(\lambda\) in diameter and 1 micron in length. In the resting muscle sarcomere, overlapping of the two types occurs (fig. 8). The actin and myosin filaments are arranged such that one myosin filament is surrounded by six actin filaments in a hexagonal structure. Each actin filament may participate in the hexagonal grouping around more than one myosin element. The actin myofibrils are attached to the Z line which marks the limits of each sarcomere. Both the actin and the myosin myofilaments are fixed in length, both at rest and during contraction. Myocardial contractile tissue has been proposed as a sliding filament model; this hypothesis appears confirmed by the studies of Sonnenblick and his colleagues and by the very different techniques used by Elliott and his associates.\(^{56-61, 220-233}\) In this model, shortening of the sarcomere occurs with the movement of the actin filaments across the myosin filaments as an interaction occurs between specific complementary sites on the respective myofibrils. This results in reduction in the length of the basic ultrastructural unit, as the sarcomere limits, marked by the Z lines, move toward one another. The volume of the sarcomere is constant and independent of its length.\(^{55-60}\) Thus, as the sarcomere length shortens, its cross-sectional area increases, and the distance between the actin and myosin filaments expands (fig. 8A). With the ultrastructural organization of the sarcomere clearly in mind, it becomes possible to explain the mechanical behavior of cardiac muscle.\(^{69}\) This phenomenon, as noted earlier, is that as the resting length of the cardiac muscle fiber is increased, there is a proportionate increase in the force developed with each contraction, up to a point (figs. 4 and 8). After the peak force is reached, further increases in the resting fiber length result in decreases in the developed force of contraction. Studies which have attempted to relate changes in sarcomere length to the function of the myocardium have demonstrated that resting sarcomere length is proportional to overall muscle length, and the maximum developed tension occurs at an ideal sarcomere length of about 2.2 microns.\(^{196, 198}\) As sarcomere length decreases below 2.2 microns with decreasing myocardial muscle length, the developed tension decreases—the “ascending limb” of the length–tension relation (fig. 8). Similar decreases in developed tension occur when the resting length of the myocardial sarcomere is increased beyond 2.2 microns—the “descending limb” of the length–tension relation (fig. 8). Progressive overstretching of the myocardial sarcomere produces a progressive decrease in developed tension until 3.6 microns is reached, at which time the developed tension falls to 0. Electronmicroscopic studies of sarcomeres stretched to this degree reveal that at this point there is no overlap of the actin and myosin filaments.\(^{196, 198}\)

A variety of hypotheses have been advanced in an attempt to explain the Frank–Starling mechanism on the basis of this interaction between actin and myosin.\(^{106, 137, 202, 205, 228}\) The definitive observations which will permit us to choose between these competing theories have not yet been made. However, the hypothesis which the reviewer finds most consistent with the observed data is that of Spencer and Worthington.\(^{202}\) In this theory, the force generated depends on the number of interacting sites between the actin and myosin filaments. At the ideal resting length of 2.2 microns there are a large number of potential sites for interaction, and the distance between actin and myosin fibrils is such that the attracting force between the complementary sites on the respective fibrils is very great (fig. 8). The net balance between the number of interacting sites and the distance over which these forces can act is maximum, producing a maximum developed force on activation. When the fiber is shorter than this ideal length, although a larger number of potentially-interacting sites are in apposition to one another, because the sarcomere volume is constant the distance between the individual actin and myosin fibrils is greater (fig. 8A).\(^{202}\) Therefore, the net force which can be generated between interacting sites is decreased to something less than the ideal maximum, as a function of the reduction in overall length of the total sarcomere. Conversely, when the sarcomere is stretched
beyond its ideal length, although the distance between actin and myosin fibrils is decreased, theoretically producing an increased potential force between any two complementary sites, the number of complementary sites in potential apposition is also decreased because the overlapping of actin and myosin fibrils is decreased, and the total force which can be generated during contraction is reduced (fig. 8B). Sonnenblick and his colleagues \(^{152,196,198}\) have demonstrated that, in the intact canine heart, the ideal sacromere length of 2.2 microns appears to correspond to the upper limit of the normal ventricular filling pressure under physiologic conditions.

Although the ultrastructural organization of the myocardial sacromere provides an explanation for the static force-generating properties of the myocardium operating under the Frank–Starling mechanism, it is important to realize that the myocardium is a dynamic engine and that to describe the Frank–Starling mechanism completely a hypothesis of contraction must consider the velocity characteristics of the force-generating process.

To return to the ultrastructural unit as the basis for the dynamic aspects of myocardial contraction, the dynamic conceptual model formulated by Spencer and Worthington \(^{202}\) on the basis of x-ray diffraction studies of skeletal muscle also provides an analysis of muscular contraction in terms of impulsive force compatible with the observed molecular structure of actin and myosin. In this model, charge transfers are seen to occur serially along a fixed number of sets of active sites per sarcomere, generating a given amount of force per site (fig. 9A). Each charge transfer occurs at only one site during a finite time interval, which represents the time for a 25Å site shift, the net difference between the spacing of complementary sites in the actin and myosin myofibrils (fig. 9B). This time for impulsive force generation, therefore, represents the molecular V\(_{max}\). \(^{222,223}\) In this analysis applied to cardiac muscle \(^{178}\) the duration of active state reflected in the time from the onset of contractile element activation to the maximum dp/dt (or the slope of the relationship dp/dt, IIT) is a function of the time interval during which the total impulsive force is generated by the contracting myocardium. The overall duration of active state may be considered to represent the sum of the times of the series of impulsive forces occurring at the molecular level (fig. 9C) and is thereby a function of the velocity–dependent constant “b” of Hill’s equation. \(^{222}\)

The use of impulsive force and its rate of delivery also provides an indication of the total mechanical energy available in each contraction. The importance of this kind of information is seen in examining the effect of increasing heart rate. Over a wide range in the isovolumetric ventricle, the total impulsive force (IIT) remains little changed although the maximum rate at which this impulsive force is delivered (dp/dt) increases with increasing frequency of stimulation. \(^{178}\) This observation suggests that over most of the normal operat-
ing range the total mechanical energy per beat is not increased by increasing heart rate, even though peak tension tends to rise (the *treppc* effect). In other words, a velocity *treppc* rather than a force *treppc* has occurred. This is consonant with the findings in isolated muscle that over a broad portion of its range, increasing frequency increases the maximum velocity of shortening (\(V_{\text{max}}\)) with little or no change in isometric force (\(P_0\)). In the study of inotropic drugs, it is possible to ascertain whether the total mechanical energy available per beat, as well as the maximum rate of delivery of this mechanical energy, is increased (fig. 7). An analysis of a specific pharmacologic or anesthetic agent with myocardial effects is then possible by determination of the rate at which it causes the myocardium to impart a given impulsive force.

The concept that myocardial contraction is a quantum process, in which a small amount of energy is liberated at each contractile site, and that the time during which the impulsive force is liberated is a function of the rate of activation of the sites, provides a useful way of visualizing the difference between the Frank-Starling mechanism and the effects produced by inotropic agents. Through the former mechanism the amount of energy at each site is fixed and the total energy liberated by a contraction is a function of the number of sites in potential apposition and their axial distance apart. Increases in the rate of activation increase the rate of charge transfer and can decrease the time during which each quantum of energy is liberated. This cannot alter the total amount of energy liberated, but it could result in a more effective summation of external force. Chemical inotropic substances might somehow alter both the rate of charge transfer and amount of energy available at each site, but not necessarily in parallel fashion. The rate at which this energy transfer occurs might be increased, just as increasing the charge on one plate of a condenser produces a more rapid rate of charge decay when the condenser is discharged. It is not clear why chemical positive inotropic agents produce a greater
force of contraction, but it may be due to the increased availability of high-energy phosphate compounds they produce.\textsuperscript{23, 24, 129} In this hypothesis as applied to cardiac muscle, the velocity-dependent aspects of contraction (represented by the $V_{\text{max}}$ of the force–velocity relationship) and the durational aspects of contraction (represented by the duration of active state, and reflected in $\Delta t \, dp/dt$ and by the slope of $\frac{dp/dt}{II}$) are different aspects of the same process. This could be, because the number of sites is fixed by the total length of the myofibrils, not by the number of sites actually in opposition.\textsuperscript{202} Therefore, the duration of active state is a function of the velocity of the activating impulse occurring serially along a fixed number of sites on a given myofibril, not by the charge transfer between complementary sites on different myofibrils.

An important corollary of this theory is that up to some maximum level the inotropic effects of a number of agents are additive with regard to velocity and force-generating properties. This is shown in figure 10, in which myocardial acceleration, reflected by the index $\frac{dp/dt}{II}$, increases both with heart rate and with the release of norepinephrine at a given heart rate produced by sympathetic stimulation, all at a constant fiber length point in the Frank–Starling mechanism. The increase in $\frac{dp/dt}{II}$ effected by heart rate is small compared with that produced by sympathetic stimulation at the same heart rates, but both are additive.\textsuperscript{178} The significance of the additive nature of inotropic effects in the functioning heart is that increases in heart rate brought about by a process not productive of a concomitant and commensurate sympathetic stimulus (an arrhythmia-induced tachycardia), may not decrease the duration of the active state of the contractile element sufficiently to permit complete relaxation after one contraction\textsuperscript{177} prior to the beginning of the successive contraction. Consequently, the weak inotropic action of heart rate increases may actually produce less developed tension, even though the maximum velocity of contraction ($V_{\text{max}}$) may be slightly increased. Incomplete dissipation of contractile-element activity prior to the initiation of a new beat at the same rate (mechanical pulses alternans) reduces the impulsive force (IT) and the velocity of myocardial force generation ($dp/dt$) obtainable from a given fiber length without changing the relationship between them.\textsuperscript{173} This is understandable if the contractile element is qualitatively unchanged, but by virtue of being partially contracted when reactivated it cannot contract as much, and consequently has less force to exert. Norepinephrine greatly increases the maximum velocity of contraction. It also increases the period of ventricular relaxation\textsuperscript{223, 224} by markedly decreasing the duration of the active state of contraction.\textsuperscript{120} In so doing, it prevents a rate-induced alteration in ventricular distensibility\textsuperscript{177} and abolishes mechanical pulses alternans.\textsuperscript{127} The fact that release of endogenous norepinephrine with reflex cardiac sympathetic stimulation produces both a small increase in $V_{\text{max}}$ secondary to the chronotropic effect and a major increase in $V_{\text{max}}$ secondary to the inotropic effect undoubtedly has a decided survival potential, since it permits a more effective contraction, and therefore a greater stroke volume, to be produced at any given fiber length by maximizing the rate and amplitude of the impulsive force generated during systole,\textsuperscript{178, 180} as well as the time available for relaxation and coronary filling during diastole.\textsuperscript{223, 224} Other inotropic agents also have an additive effect in increasing the myocardial force–velocity relationship.\textsuperscript{16} The ability to obtain a quantitative evaluation of the force and velocity aspects of myocardial contraction should permit the physician to obtain a maximum inotropic effect for any given myocardium by the proper choice of fractionate doses of any of a variety of inotropic agents.

The Effects of Occult and Overt Myocardial Failure on Myocardial Mechanics

For the surgeon who must undertake a difficult operative procedure in a patient with depressed myocardial function, and for the anesthesiologist who must be responsible for anesthesia and circulatory pharmacology during this critical period, it is important to estimate
crease in the myocardial force–velocity relationship occurs at all therapeutic dose levels, and negative inotropic effects are additive, just like positive ones.\textsuperscript{179} Myocardial shortening (fig. 11B) is also decreased, which results in a reduced cardiac ejection occurring from the depressed myocardium, especially if the afterload is maintained at or near control values. The myocardial work–load function is described by a lower work curve which has a diminished maximum work level (fig. 11C). Also, this point of maximum work occurs at a substantially reduced afterload. This is analogous to the diminished stroke work which occurs at a lower aortic resistance in the failing heart, compared with the normal heart. As in the depressed papillary muscle, increases in aortic resistance in the failing heart frequently result in decreases in external cardiac work although, as Ross et al.\textsuperscript{152} have demonstrated in the intact heart, the resultant increases in diastolic volume, by increasing fiber length and developed tension, may actually result in an increase in internal work so that the total work may be little changed. These studies suggest that even at constant diastolic volume the fraction of work done in stretching the series elastic element is increased by failure, while contractile element work is decreased.

The effects of pentobarbital on myocardial contractility in the intact heart of an animal on right-heart bypass with controlled cardiac output and heart rate (fig. 12) show that the decrease in the maximum velocity of contraction in the force–velocity relationship\textsuperscript{152, 179} has correlates in 1) a decrease in the intensity of active state, represented by a fall in the level of dp/dt from the same or greater diastolic fiber length; 2) an increase in the functional aspects of the active state, represented by an increase in $\Delta t$ dp/dt; and 3) a fall in the acceleration of myocardial force, represented by a fall in the ratio $\frac{dp}{dt}$. Administration of a digitalis-like preparation (in this case acetyl strophanthinidin) which increases myocardial force–velocity relationships\textsuperscript{152, 179} increases the intensity of the active state from any given fiber length; decreases the duration of the active state, reflected in the decreased $\Delta t$ dp/dt; and increases the acceleration of myocardial contractility.

The basal myocardial contractile state. Equally important is a full understanding of the effects on myocardial mechanics of the various surgical and pharmacologic interventions likely to be used.

As a tutorial model, it may be useful to examine in detail the myocardial depression produced by pentobarbital.\textsuperscript{179} Its mechanism appears to be characteristic of agents which depress myocardial contractility.\textsuperscript{66, 132, 165, 179, 206, 207} Pentobarbital brings about its negative inotropic effect by depressing the force–velocity relationship, so that both the maximum velocity of shortening ($V_{max}$) obtainable by the unloaded muscle and the maximum load ($P_n$) which can be lifted by shortening muscle are decreased (fig. 11A). This can be related to decrease in the rate of intraventricular pressure development (dp/dt) and to a fall in the systolic pressure generated by the intact heart (fig. 12). The extent of this depression appears to be a function of dosage, but some de-
force, as shown by the increase in the isometric
time-tension index.\textsuperscript{179} This reversal of myo-
cardial depression produced by acetyl stro-
phanthidin results in an increase in the propor-
tion of the diastolic volume ejected during
systole. It thereby produces an increase in
cardiac output and systolic pressure in the pa-
tient with a failing heart.

**THE RELATION OF HEMODYNAMIC FAILURE
to the Myocardial Contractile State**

The most commonly used qualitative index of
myocardial failure is the ventricular func-
tion relationship which relates the alteration
in stroke work to end-diastolic filling pres-
sure.\textsuperscript{158, 263} A comparison of the effect of failure
on a direct measure of myocardial con-
tractility (the isometric time-tension index)
with the resultant alterations in external myo-
cardial work, as expressed by the ventricular
function (VF) curve, is shown in figure 13.\textsuperscript{179}
In the study from which figure 13 was taken,
the heart was paced at a constant rate and the
left ventricle was forced to accept increments
in diastolic volume. After the control ventricu-
lar function curve (curve 1), cardiac efferent
sympathetic (stellate) nerve stimulation was
carried out with resultant displacement of the
ventricular function curve to the left, so that
more stroke work was done from a lower filling
pressure. A marked decrease in the $\Delta \frac{dp}{dt}$
and a concomitant increase in the isometric
time-tension index ($\frac{dp}{dt}$ \textit{IIT}) was observed,
indicating that myocardial contractility increased.
With cessation of stimulation, both the VF
curve and the isometric time–tension index re-
turned to control values. After re-establish-
ment of the control level, two equal doses of
pentobarbital (curves 2 and 3) were adminis-
tered, and after each dose the VF curve and
the isometric time–tension index were deter-
mimed. There was a shift in the VF curve to
the right with each dose of pentobarbital, so
that a higher ventricular filling pressure was
required to perform a given amount of stroke

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{Effect of increasing pentobarbital dosage on isometric
time-tension relationships in the intact canine heart. Right heart bypass at
constant cardiac output and heart rate. Between A and B: 120 mg of
Na pentobarbital admin-
istered iv. Between B and C: 120 mg of Na
pentobarbital admin-
istered iv. Between C and
D: 0.5 mg of acetyl stro-
phanthidin administered
iv. Shaded area design-
ates fractional IIT based
on 1.5 times the time
from the r wave of the
ECG (lead II) to maxi-
mum $\frac{dp}{dt}$. $\Delta \frac{dp}{dt}$ =
maximum rate of de-
velopment of isometric
tension. $\Delta t \frac{dp}{dt}$ = time
from r wave to maximum
$\frac{dp}{dt}$. Time lines 0.02
second. (From Siegel
and Sonnenblick,\textsuperscript{179} with
permission of the publish-
ern.)}
\end{figure}
work, indicating an increasing degree of hemodynamic failure. There was also a fall in the isometric time-tension index to an increasingly lower constant, indicating a decrease in myocardial contractility. The administration of acetyl strophanthidin (curve 4) produced a shift to the left in the VF curve, compared with the two preceding pentobarbital curves, and also induced a return towards control levels of the index \( \frac{dp/dt}{H/I} \). The isometric time-tension index reflects the level of the myocardial contractile state independent of end-diastolic fiber length or volume for the entire ventricular function curve.\(^{176-180}\) It is clear that either this index or the instantaneous tension-velocity-length relationship which measures changes in \( V_{\text{max}} \)\(^{39, 40, 72, 76, 125, 192} \) could have predicted the inability of the depressed myocardium (curve 3) to handle an increased volume load without elevating its end-diastolic pressure (LVED) to failure levels, from a single determination of myocardial contractility before cardiac failure was produced by transfusion.

Agents which permit positive alterations in the inotropic mechanism by increasing \( V_{\text{max}} \) and decreasing duration of the active state enable the depressed myocardium to compensate for the stress of an acute volume load.\(^{182, 183, 177, 178}\) Increasing contractility also permits the depressed myocardium to compensate for a pressure load.\(^{171, 179, 181}\) As is shown in an animal on right-heart bypass (fig. 14) at constant cardiac output, when myocardial depression was produced by the administration of pentobarbital the heart was unable to compensate for a sudden increase in arterial resistance produced by cross-clamping the aorta. This stress (similar to that produced during resection of an aortic aneurysm) resulted in the heart’s responding to the mechanical increase in arterial resistance by accepting a

**Fig. 13.** Comparison of pentobarbital-induced myocardial depression on ventricular function curve (panel A) and isometric time-tension relationships (panel B) showing the effect of acetyl strophanthidin. Right heart bypass. Heart rate paced at 177/min. Cardiac output increased in equal steps from 870 ml/min to 1,790 ml/min except in curve 3, where an additional point at 630 ml/min was also obtained. (From Siegel and Sonnenblick.\(^{129}\) with permission of the publisher.)
small increment in diastolic volume with each beat, increasing the arterial pressure generated by the device of increasing the fiber length and LVED progressively. In the depressed myocardium (A) no leveling off of end-diastolic pressure occurred, and the LVED rose to failure levels. However, following the administration of norepinephrine (B), with a resultant increase in myocardial contractility, quantified in this experiment by the index \( \frac{dp/dt}{IIT} \), the heart was able to withstand the stress of aortic occlusion. In this instance, when the resistance load subsequently was applied, the heart achieved a higher systolic pressure at the expense of only a small increase in diastolic volume, mirrored by the small increase in LVED. Further, this small elevation in LVED was maintained and even declined at a time when arterial pressure continued to rise. In contrast to the depressed myocardium, there was no progressive increase in LVED in response to the maintained arterial pressure load. Clearly, in panel A, a depressed myocardium was stressed into demonstrating its limited capacity and consequently showed evidence of hemodynamic failure. In panel B, however, compensation had been achieved by the administration of an inotropic agent, which has been shown to increase the myocardial \( V_{max} \). The depressed myocardium shown in the first panel was clearly a "failure" myocardium even before it was stressed. The stress merely demonstrated the latent failure which could have been predicted from initial determination of the isometric time–tension relationship or the instantaneous tension–velocity relation. The compensation occurring after the administration of an inotropic agent could have been predicted from the same indices before the stress demonstrated it. Similar reversal of myocardial failure has been related to quanti-

**Fig. 14.** Prediction of hemodynamic failure from the quantification of the myocardial isometric time–tension relationship. Right heart bypass. Faced heart 187/min. Cardiac output 1,370 ml/min. LV indicates left ventricular end-diastolic pressure; LV, full scale left ventricular pressure; AP, aortic pressure. Large number on abscissa under each rapid tracing represents calculated value of \( \frac{dp/dt}{IIT} \). A, myocardium depressed with 240 mg of pentobarbital. Aortic occlusion, at constant cardiac output, between arrows. B, myocardial compensation achieved by 40 \( \mu \)g of levaterenol immediately following A. Aortic occlusion, at constant cardiac output, between arrows. Rapid tracing 100 mm/sec. Slow tracing 1 mm/sec. (From Siegel and Sonnenblick,\(^{19}\) with permission of the publisher.)
tative increases in the contractile state occurring after cardiac sympathetic nerve stimulation, and after administration of isoproterenol, angiotensin, calcium ion, or a variety of digitalis preparations.122, 171, 175, 181

A reduction in the maximum velocity of the force-velocity relationship, similar to that produced by negative inotropic agents such as pentobarbital,122, 179 halothane,267 and methoxyflurane,165, 266 has been demonstrated to be characteristic of the development of myocardial failure secondary to hypothyroidism,22 and progressive myocardial hypertrophy.289 A reduction in myocardial $V_{\text{max}}$ is probably also the cause of the decrease in the velocity characteristics of the myocardium which occurs in association with ischemia.99

**THE EFFECTS OF HYPOTENSION ON MYOCARDIAL MECHANICS IN FAILURE**

A fall in myocardial contractility may be associated with a lowering of arterial blood pressure. The resultant decrease in the resistance component of the afterload may help the failing heart in that it permits the depressed myocardium to operate from a more advantageous point in the force-velocity relationship (fig. 11). This enables the myocardial fibers to shorten to a greater extent and at a greater velocity than would be possible had impedance to ventricular ejection remained constant, thus increasing the proportion of the total afterload contributed by stroke volume.108, 161, 193, 215 Since the active state of the myocardial contractile element occurs earlier than peak force development,167, 190 the reduction in the instantaneous impedance to ventricular ejection, by reducing the afterload earlier in contraction (fig. 2), also permits a further increase in both ejection velocity and stroke volume without change in the intrinsic myocardial contractile state.215 For these reasons, negative inotropic anesthetic agents like methoxyflurane and halothane, which also decrease peripheral vascular resistance,9, 63, 145 may produce far less decrease in cardiac output than would be expected from the concomitant reductions in myocardial contractility. This undoubtedly has some survival advantage, since it permits the intact heart to maintain a greater forward output than would be possible if aortic pressure remained high. Therefore if myocardial depression is severe enough, decreasing the afterload by reducing either the volume or the pressure component may actually permit increased myocardial work or power to be achieved by a failing heart, since it permits the depressed myocardium to operate at a work-load point nearer to its maximum work capacity (fig. 11).

**Considerations in the Choice of Vasopressor Drugs in Myocardial Failure**

An unrecognized depression of myocardial contractility secondary to diffuse myocardial disease may be associated with refractory hypotension in the surgical patient when the heart has been further depressed by anoxia, anesthetic agents, or endotoxin toxicity.86, 87, 176 Therefore, it is important that both surgeon and anesthesiologist consider the effects on myocardial contractility of the agents commonly used to alter vascular tone before instituting any therapeutic program aimed at combating arterial hypotension. In the treatment of circulatory shock it is sometimes clearly in the patient's best interest to utilize selectively either an arterial vasocostrictor 13, 34, 44, 51, 91-92, 100, 168, 211 or an arterial vasodilator 4, 22, 62, 63, 121, 176, 177, 212. However, it is not well understood that the incorrect choice or use of a vasopressor agent to elevate blood pressure may actually increase myocardial failure and thus prejudice survival.34, 91, 92, 151, 171, 181, 211 Conversely, it is important to understand when the shock-producing myocardial lesion results not from generalized depression of contractility but from a localized reduction in coronary flow secondary to an infarct produced by atherosclerotic coronary occlusive disease, a vasodilator agent may be extremely deleterious even if it has a positive inotropic action.22

**THE MYOCARDIAL EFFECTS OF VASOCOCTRICTOR THERAPY**

The fundamental consideration in the use of a vasopressor agent for hypotension associated with depressed myocardial contractility is the relative proportion of central cardiac inotropic activity to degree of peripheral vasoconstriction possessed by the drug.34, 81, 100, 234 The cardio-
Fig. 15. Comparison of norepinephrine and methoxamine on myocardial isometric time-tension relationships in the intact dog in which baroreceptor deafferentation had been achieved by bilateral vagus section and carotid denervation. No attempt was made to control cardiac output or heart rate. From above downward in each tracing are shown dp/dt, full-scale left ventricular pressure (LVP), and the ECG. The shaded area indicates the fractional ITT. The LVP pressure scale is indicated in mm Hg between each two panels. Time lines 0.02 sec. (From Siegel et al. with permission of the publisher.)

Dynamic activities of a vasoconstrictor agent with a strong cardiac inotropic action (norepinephrine) and a vasoconstrictor agent which has little or no ability to increase myocardial force-velocity relationships (methoxamine) are compared in figure 15. In this animal, in which reflex sympathetic changes had been abolished, the levels of aortic pressure increment achieved by the two drugs were approximately the same. However, the duration aspects of contraction and the velocity of isometric pressure development were much different, reflecting differences in ability to increase myocardial force-velocity relationships and to decrease the duration of the active state. A vasopressor agent without cardiac inotropic activity, such as methoxamine, may produce hemodynamic failure in the heart with depressed contractility, even though arterial blood pressure and coronary flow increase. On the other hand, the use of a vasopressor agent with a positive cardiac inotropic action enables the depressed heart to compensate for the increased load imposed by peripheral vasoconstriction without producing cardiac failure. Effects similar to that produced by a vasoconstrictor agent without cardiac inotropic activity have been produced by norepinephrine, or catecholamine-releasing agents with vasoconstrictor properties, when these drugs were given after the introduction of beta-adrenergic blockade, which prevents the sympathomimetically-induced alterations in $V_{\text{max}}$. Similarly, beta blocking agents induce congestive cardiac failure in patients in whom myocardial depression has been compensated by an increase in sympathetic tone.

The use of the hypertensive polypeptide angiotensin as a vasoconstrictor agent is also not without hazard. Although this agent may possess a weak intrinsic inotropic effect of its own, its major action in increasing myocardial force-velocity relations appears to be through release of myocardial catecholamines, and can also be markedly reduced by the use of a beta-adrenergic blocking agent, or in the presence of myocardial catecholamine depletion. In addition, in experimental preparations angiotensin can induce an initial profound coronary artery vasoconstriction; this may be the etiology of the electrocardiographic
evidence of myocardial ischemia which can accompany its use.

In the consideration of the use of a specific cardiac inotropic agent it is helpful to keep in mind the interrelations shown in figure 16, between myocardial contractility (panel I), the external work-load relationship of the ejecting heart (panel II), and the length–tension relationship of the isometrically contracting heart (panel III). The important features of this graphic analysis comparing the heart in failure and after the administration of an inotropic agent are: 1) at a given contractility (V_max), reflected by the slope (panel I) of the isometric time–tension relationship \( \frac{dp/dt}{I/T} \), the heart is able to develop a maximum isometric tension (panel III) for each diastolic volume at the expense of maintaining a given end-diastolic pressure (LVED); 2) at any given diastolic volume, the heart may either contract isometrically (panel III) and do no work, or eject a fraction of its diastolic volume against the aortic pressure (afterload) and do an amount of work (panel II) which in turn depends upon the aortic resistance load against
which the ejection occurs. Thus, the external work which the heart can do at a given diastolic volume and contractility is a load-dependent curve (panel II), with the maximum work occurring at an afterload level (aortic pressure x stroke volume) which is always less than the maximum isometric tension of which the heart is capable (panel III).

The compensated heart (inotropic) can accept an increased pressure or flow load with little or no increase in fiber length because there is a relatively wide range over which increasing load is productive of increasing work (panel II, curve A'), and because the point at which further increments in afterload produce decreases in work is at a relatively high load level, probably never reached in the normal heart. This allows for large changes in ventricular work without the necessity of impinging on the reserve provided by the Frank-Starling mechanism. In the decompensated heart (failure), on the other hand, the range of increasing work in response to increasing afterload is relatively narrow (panel II, curve A), and the point of diminishing return is at a low load level. Consequently, in order to do the same work at a given afterload as a compensated heart, the depressed heart must significantly increase its fiber length—unless extrinsic factors such as reflex sympathetic stimulation or drug-induced catecholamine release can produce an increase in the basic inotropic state of the myocardium.

The failing heart, therefore, must invoke the Frank-Starling reserve. The less inotropic capacity the heart has, the more it must depend on its ability to increase fiber length. In the intact animal or man reflex vasoregulatory mechanisms tend to stabilize aortic pressure by altering chronotropic and inotropic influences to match the load imposed by alterations in peripheral vasocostriction and venous return. If the former two influences do not match the latter two, fiber length increases. Hemodynamic failure occurs when a gross disproportion in favor of the load factors compared to the inotropic effects is achieved, so that very great increases in fiber length are necessary to allow a work level which can handle the imposed afterload. Frequently, in the severely depressed myocardium, no increment in fiber length will permit a maximum work point sufficiently far to the right to compensate for the imposed afterload by increasing work production, so that diminished work occurs even from a markedly increased fiber length (panel II, curve C).

With this in mind, it can be seen that the effect of a positive inotropic vasconstrictor agent such as norepinephrine, metaraminol, or angiotensin will be more important in the depressed "occultly failing" myocardium, which in spite of a markedly increased fiber length (panel III, point B) is already working near the peak of its work-load relationship (panel II, curve B) than in the normal heart. In the failing heart, by allowing the myocardium to shift to an improved length-tension relationship (from failure curve A, B, C, to inotropic curve A', B', panel III) inotropic agents enable the heart to achieve greater maximum work at a higher aortic pressure (afterload) from any given diastolic fiber length (panel II, curves A' and B'). This increased contractility is demonstrated by an increase in the isometric time-tension index (from slope A, C, B to slope A', B', panel I) and reflects an increase in the maximum velocity of shortening of the contractile element (Vmax). Further, at any fiber length and aortic pressure, the increased myocardial shortening, the increased rate of isometric force development (dp/dt, panel I), and the greater velocity of shortening enable the inotropic heart to eject a larger fraction of its initial volume at each stroke, and thus permit it to reduce its initial fiber length in subsequent beats, moving from point B on the failure curve toward point A' on the inotropic length-tension curve (panel III). This would be of enormous advantage to the myocardium already on the plateau (panel III, point B) or on the descending limb (panel III, point C) of its length-tension relationship, where further increases in diastolic volume produce either no change or only decreases in developed tension and dp/dt.

Increasing aortic pressure (afterload) at a given diastolic volume without an inotropic effect (panel II, curve A), as is done by methoxamine, may force the depressed myocardium to operate from a point other than the maximum work point in its work-load relationship,
so that less external work is done as the resistance load increases. As aortic pressure (afterload) increases at a given diastolic fiber length, myocardial shortening and the velocity of myocardial shortening decrease. Consequently, the fraction of the diastolic volume ejected at each stroke decreases as a function of the increasing aortic pressure, and the initial fiber length increases, moving from point A to point B on the failure length–tension curve) (panel III). This, in turn, will enable the myocardium to shift to an increased work–load relationship, changing from curve A to curve B (panel II), where the point of maximum work is at a higher aortic pressure (afterload).

However, even though myocardial work has been increased, no contractility change has occurred; both of these work curves are still failure curves, and they have identical isometric time–tension relations and the same $V_{\text{max}}$ (slope A, C, B, panel I). In the depressed heart, the myocardium may already be operating at the top of its length–tension relationship (panel III, point B). This may mean that overt hemodynamic failure is produced as the heart is pushed onto the flat or descending limb of the failure length–tension curve (Panel III, point C). In addition, the work–load relationship (panel II, curve C) corresponding to this point on the descending limb of the myocardial length–tension curve is such that less external work can be performed even though the heart is operating from a larger diastolic volume. Artificial maintenance of aortic pressure with the resultant cardiac dilatation while on the descending limb of the myocardial length–tension curve could result in irreversible overstretching of the myocardial sarcomeres.155, 194, 198

Further, as is shown in figure 17, the use of a hypertensive agent such as methoxamine, which fails to induce a compensatory inotropic effect of its own, will result in a net decrease in contractility secondary to the withdrawal of cardiac sympathetic activity.55 In the already depressed and occultly failing myocardium with borderline contractility, a small further decrease in contractility may make overt hemo-
dynamic failure inevitable. These factors may explain the rapid development of hemodynamic failure which often accompanies a hypertensive crisis in the patient with myocardial hypertrophy even when coronary occlusion does not occur.

In the presence of an intact carotid sinus and aortic baroreceptor mechanisms, in contrast to methoxamine, positive inotropic vasoconstrictor agents such as norepinephrine, metaraminol, and angiotensin, can result in a net positive inotropic effect on the myocardium even though their hypertensive actions also produce reflex cardiac sympathetic withdrawal. However, it is important to stress that while infusions of norepinephrine and metaraminol at therapeutic levels cause a net increase in myocardial contractility in man, at present it is not known whether clinical doses of angiotensin used to combat hypotension produce a net increase or decrease in contractility, although there is experimental evidence of an increase in the contractile response to oligemic shock. That the positive inotropic response of the myocardium to angiotensin administration can be at least partially blocked by a beta-adrenergic blocking agent indicates its action may be in large part through direct myocardial catecholamine release. In addition, the depression of both the isometric time—tension relationship and the ventricular function curve occurring with prolonged angiotensin infusions suggests that myocardial catecholamines may be depleted in a manner similar to tyramine.

This further suggests that in patients in whom the myocardium is depleted of catecholamines, as with reserpine, with some anesthetic agents, or in chronic congestive cardiac failure, the use of angiotensin, metaraminol, or other agents which rely for any part of their actions on the release of myocardial stores of catecholamines may be contraindicated, since in the absence of inotropic action, the increased afterload and possible coronary vasoconstriction induced by these drugs may make their use extremely hazardous. Indeed, Ross and Braunwald have demonstrated marked impairment in ventricular function relationships of patients with left ventricular failure who were stressed by the administration of angiotensin. This group of patients had reduced myocardial stores of catecholamines. Similarly, Gunnar and his colleagues showed that in patients with shock secondary to acute myocardial infarction norepinephrine, which has both alpha- and beta-adrenergic actions, has a hemodynamic advantage over methoxamine, which cannot alter myocardial contractility. Furthermore, not only does the quantity of norepinephrine released by sympathetic nerve endings in the myocardium depend on the frequency of impulse traffic in the cardiac sympathetic efferent nerves, but infusion of norepinephrine can increase both the quantity of catecholamine stored at the nerve endings and the amount released by depolarization of these nerves. Therefore, when the patient has an absolute or relative depletion of myocardial catecholamine stores, the physician must choose only those catecholamines with an intrinsic beta-adrenergic ability to increase myocardial force—velocity relationships, if the already-present myocardial contractility is not to be exacerbated by the reflex withdrawal of sympathetic efferent tone.

The Myocardial Effects of Vasodilator Therapy

The use of a positive inotropic agent with exclusively beta-adrenergic properties, isoproterenol, has also been of considerable value in the treatment of a variety of types of primary heart disease and in some forms of shock. The use of isoproterenol can both increase myocardial force—velocity relationships and decrease the duralional aspects of contraction reflected in the isometric time—tension relationships. Isoproterenol increases myocardial $V_{max}$, maximum rate of development of isometric tension (dp/dt) from any given fiber length, and the ratio $\frac{dp}{dt}$ II T These changes (fig. 16) results in a shift from the failure length—tension relationship characterized by curve A, B, C, in
panel III to the inotropic relationship characterized by the curve A', B'. This inotropic shift permits the myocardium to generate a higher tension from any given diastolic volume. Following valve opening, by increasing contractility isoproterenol also permits an increased velocity of shortening, which enables the heart to eject a larger fraction of its diastolic volume. With regard to afterload effects, isoproterenol produces peripheral vasodilatation, which results in reduction in the impedance to flow in the aortic bed. Since this also reduces the initial afterload, it allows the myocardium to operate from a more advantageous point on its already-improved force-velocity relationship. As the resistance component of the afterload decreases, myocardial shortening, and consequently ejection, will increase further, also producing a larger stroke volume in a manner not dependent on the contractile state. Since external work represents stroke volume times the integrated pressure against which this volume is ejected, there may be an initial decrease in myocardial work as the afterload is reduced, provided the heart is working on the ascending portion of its work-load relationship (panel II). In the myocardium which is working at a disadvantageous load point on the descending portion of its work-load relationship, reduction in afterload may even result in increased stroke work as the heart operates nearer the maximum work point. This latter effect would also result from the use of noninotropic alpha-adrenergic blocking agents or from spinal anesthesia, which also reduce the impedance to ventricular ejection. Generally, however, the net result of the increased myocardial contractility and the reduced aortic impedance produced by isoproterenol is to reduce diastolic fiber length so that, in spite of augmented stroke volume, the final equilibrated load may be very similar to that seen in the control state; there is often no significant alteration, or a small increase, in the external myocardial work. However, since the inotropic effects of this agent permit the heart to shift from a failure work curve (curves A, B, or C, panel II) to an inotropic series of curves (curves A', B', panel II), the heart is better able to handle the required work, since the maximum work point has been shifted to a higher afterload level than was possible in the failure state.

All positive inotropic agents studied increase myocardial oxygen consumption as a function of the increase in the rate of development of isometric tension from a given length (dp/dt). In spite of this, Corlin has shown that this drug reduces myocardial lactate production in patients with severe coronary artery disease and congestive cardiac failure, and suggests that myocardial oxygenation improves during infusion of isoproterenol. This may occur because an inotropic agent, by reducing the diastolic volume of the ventricle, causes a net reduction in myocardial wall tension even though it increases contractile force, since the increase in $V_{max}$ permits the myocardial fiber to operate from a lower point in its length-tension relationship. In a dilated heart the net result of an increase in dp/dt on the basis of the inotropic mechanism and a decrease in dp/dt on the basis of a more favorable position on the Frank-Starling curve can be a reduction in overall oxygen consumption.

The Myocardial Effects of Digitalis

Although other agents such as glucagon and calcium have intrinsic positive inotropic effects, the major noncatecholamine drugs which have important effects on myocardial force-velocity and isometric time-tension relationships are the digitalis and digitalis-like compounds. These vary considerably with regard to potency and rapidity of action. However, all appear to be capable not only of increasing the contractility of the failing myocardium but also of increasing force-velocity relationships in the normal human heart. The actions of this class of inotropic agents with regard to effects on myocardial length-tension and work-load relationships are similar to the actions of other inotropic agents. While digitalis preparations are not vasoconstrictor agents on a par with the alpha-adrenergic catecholamines, they can produce significant arteriolar vasoconstriction both experimentally and in man. The interaction of digitalis preparations with other agents which also alter myocardial force-velocity relationships is of inter-
est. While pharmacologic agents which reduce the beta-adrenergic properties of catecholamines block digitalis-induced cardiac arrhythmias, there is no evidence that myocardial catecholamine depletion either by administration of reserpine or by chronic cardiac denervation prevents the isotropic action of digitalis in the intact animal. In general, the isotropic actions of digitalis preparations are additive with those of other agents capable of increasing myocardial force-velocity relationships. Both the isotropic and the arrhythmic properties of digitalis preparations can be increased by treatment with beta-adrenergic catecholamines, by decreases in serum potassium, or by increases in serum calcium levels. Glucagon, in association with digitalis preparations appears to enhance the positive isotropic effect without chronotropic stimulation. It is important to stress that in the patient who has depressed myocardial contractility but is not in overt failure a major isotropic effect of digitalis preparation can be effected at a dose level which is less than that required for prolongation of conduction at the atrioventricular node. Digitalis preparations can reverse the reduction in myocardial contractility caused by halothane anesthesia and the depression of myocardial force-velocity and isometric time-tension relationships produced by barbiturates or by administration of E. coli endotoxin. Clinically, digitalis permits improved ventricular function in patients with severe sepsis and in patients with hyperdynamic cirrhotic liver disease. There is evidence that prophylactic or intraoperative digitalization may permit patients with evidence of myocardial disorders to withstand the stresses of anesthesia and surgical operation more effectively, especially the elderly and especially when these procedures involve operations on the myocardium itself.

The Heart as Muscle and Pump in Health and Disease

In considering the role of myocardial function as a determinant of the prognosis of the critically-ill patient who is to undergo anesthesia and surgical operation, it is important to re-emphasize that at any specific level of myocardial contractility the patient’s ability to compensate for an external stress is dependent on the interaction of the intrinsic myocardial state with extrinsic vascular factors which affect the role of the heart as a pump. The muscular function of the heart can be altered by agents which change the myocardial force-velocity relationship. These include the level of chemoreceptor- and baroreceptor-induced reflex sympathetic nerve activity in the cardiac efferent nerves, as well as the quantity of myocardial catecholamines available for release at the receptor site, the levels of adrenal medullary and thyroid function, and the presence of a variety of direct-acting or reflex-mediated positive or negative inotropic stimuli of a physiologic nature, including hypoxemia, hypercarbia, and acidosis. Pharmacologic agents with or without direct myocardial effects may induce alterations in myocardial contractility by altering adrenergic activity, with resultant inotropic effect. Anesthetic agents like diethyl ether and cyclopropane appear to increase circulating levels of norepinephrine by direct and reflex effects on the sympathetic nervous system, whereas halothane has been reported to reduce the activity in sympathetic pathways. Thiopental, which has a direct myocardial depressant effect, also appears to result in sympathetic stimulation accompanied by transient increases in circulating catecholamines. In addition, both cyclopropane and diethyl ether have been reported to reduce the Starling relationship between forward output and ventricular filling pressure in an isolated heart-lung preparation, which suggests that they may also bring about direct negative inotropic effects. Exercise also produces powerful reflex inotropic effects on the myocardium, even when rate changes are held constant by cardiac pacing. Intrinsic myocardial function can also be altered by changes in the rate and the rhythm of myocardial contraction and by the degree of dysynergy or dyskinesis of ventricular contraction. The latter may include the actual loss of myocardial substance, such as occurs following a myocardial infarction. Restriction of the level of
coronary blood flow, if at ischemic limits, may also produce negative inotropic effects.

The pump functions of the myocardium are influenced by inflow factors which alter the relative position of the individual myocardial fiber in the Frank–Starling relationship, and by outflow factors which alter the heart’s operation on a given force–velocity relation. The inflow factors include the adequacy and distribution of circulating blood volume, which contributes to the level of ventricular end-diastolic volume. The end-diastolic volume thus is influenced by gravitational forces, which may promote sequestration of blood in dependent areas of the body and by anesthetic agents, which alter the normal reflex vasoconstrictor mechanisms. Alterations in intrathoracic pressure, such as may occur with positive-pressure respiration or in the presence of pneumothorax, as well as alterations in intrapericardial pressure, may impede venous return to the heart and in this way reduce end-diastolic volume and resting myocardial fiber length at any given level of contractility. In a similar fashion, hemorrhage and volume replacement can induce alterations in the capacity of the venous system and can materially influence the amount of blood available for diastolic filling, as can the presence of muscular exercise with the attendant pumping action of skeletal muscle. Connections between the arterial and venous systems, such as may occur with a major arteriovenous fistula or in the hyperdynamic state occurring in severe sepsis or in cirrhotic liver disease, can produce increased venous return and consequently alter myocardial fiber length. Abnormalities in effectiveness of the atrial contribution to ventricular filling, occurring because of inefficiency or asynchrony of atrial contraction or because of valvular abnormality between atrium and ventricle also influence operation under the Frank–Starling relationship, and acute obstructive phenomenon occurring in the presence of pulmonary embolus can produce disparate levels of diastolic filling in the two sides of the heart.

On the outflow side, factors which affect the resistance to ejection from a given ventricle can change the afterload and thus produce alterations in both myocardial shortening and velocity of shortening, altering the ejected volume. These would include obstructive phenomena or insufficiency at either the pulmonary or aortic valves, the presence of a massive pulmonary embolus, distal constriction of either the pulmonary artery or aorta, such as might occur with a coarctation, and alterations in the level of arterial vasconstriction produced either reflexly or secondary to toxic, anesthetic, or pharmacologic interventions.

With all of these factors in mind, in considering the pattern of alterations present during a change in physiologic state it is clear that the application of quantitative methods to clinical evaluation of net myocardial condition is an absolute necessity if we wish to understand the individual patient’s response to the stress of anesthetics and surgery.

Quantification of the Myocardial Contractile State in Man

Although the details of the myocardial contractile response have been laid out precisely on the basis of extensive animal studies, one of the most difficult problems facing the physician responsible for the care of the critically-ill patient is evaluation of myocardial contractile function in a rapid and reliable manner which does not expose the patient to undue risk. Adequate care of such patients necessitates an estimate of myocardial muscle function as distinguished from myocardial pump function, since in many critical illnesses significant increases in cardiac output can occur when myocardial contractility appears to be deteriorating. Indeed, in a number of high-output shock states such as that associated with septic shock and the hyperdynamic state seen in severe hepatic cirrhosis with portal hypertension, high-output cardiac failure is often the event which leads to the patient’s demise.

Numerous investigators have tried to solve the problem of obtaining a quantification of myocardial contractility in man. A variety of
ingenious techniques have been devised. Most notable are the methods involving instantaneous tension–velocity–length relationships in the intact heart which have been utilized by Glick et al.,72 and Gault and his colleagues.72 These, while providing precise information, are very difficult to perform in the critically-ill patient, since they involve either previous surgery,76 or the introduction of potentially-hazardous volumes of contrast material into the left ventricular chamber.72 The determination of isometric time–tension relationships and the related functional aspects of myocardial force development devised by Siegel et al.180 also offer a quantitative measure of the level of myocardial contractility independent of considerations of fiber length. However, at present this technique requires the introduction of a micromanometer catheter into a ventricular cavity. In the evaluation of right ventricular dynamics, this can be done by flow-directed passage of the catheter using the intracardiac electrodiagram for control, thus obviating the necessity for extensive radiologic facilities.49,50,177 However, the size and characteristics of the presently-available catheter-tip manometer limit its use in the critically-ill because of the fear that the presence of such a large foreign body in the ventricle may predispose to ventricular arrhythmias. Recently, experimental studies of the dynamic aspects of the thoracic-impedance plethysmographic pulse172 have suggested that information concerning the functional aspects of myocardial contraction may be obtained by this nondestructive technique, and that in combination with a simultaneously-obtained central sphygmographic pulse, it may reveal information about the level of the myocardial force–velocity relationship and the nature of the instantaneous impedance to ejection.

All of the techniques of evaluation of the myocardial contractile state which enable separation of the effects of myocardial operation along the Frank–Starling mechanism from those induced by alterations in the inotropic mechanism show that values in resting patients with normal, or minimally abnormal, myocardial status appear to cluster about a normal range.72,74,180,192 Drug- or exercise-induced increases in contractility produce significant shifts to higher values.72,76,95,180,192 and patients who have severe myocardial hypertrophy or myocardial failure show significant decreases from the normal range of contractility levels measured by either determinations of instantaneous tension–velocity relations64,72 or right ventricular isometric–time–tension relations.180

One of the most important observations with respect to the quantification of myocardial contractility has arisen from the cineangiographic studies of Gorlin and his colleagues.93 These have resulted in the concept that in the presence of severe coronary artery disease, with ECG evidence of myocardial changes, the contractility of the entire ventricle may not be uniform. Rather, there may exist segments of ventricular myocardium with varying degrees of contractility, ranging from areas completely replaced by fibrosis secondary to infarction, to areas which merely show decreased or abnormal velocity characteristics. In many of these patients zonal coronary venous abnormalities in myocardial lactate metabolism, suggesting local ischemia, were noted to correspond to the zones of myocardial contractile abnormalities seen on ventriculography. Localized disorders of myocardial contraction appear characteristic of this form of ischemic cardiomyopathy and do not seem characteristic of the response to generalized myocardial depressants. However, agents which produce generalized depression in myocardial contraction can worsen this type of localized myocardial abnormality. The development of myocardial failure in the presence of localized disorders of myocardial contraction appears to be in part related to the lack of capacity for coordinated contraction. This dyskinesis produces a greater reduction in ventricular ejection than might be present with a uniform depression of the force–velocity relationship. Therefore, in localized ischemic myocardial determinations of myocardial force–velocity or isometric time–tension relationships based on total ventricular contraction may be in error in revealing the exact quantitative extent of myocardial depression. The development of on-line methods for quantifying the nature and extent of these zonal disorders of myocardial contractility represents one of the most chal-
Fig. 18. Comparison of ventricular function relationships and isometric time-tension relations in a patient in hyperdynamic septic shock. *Top*, right ventricular stroke work plotted as a function of right ventricular end-diastolic pressure in the patient before and after infusion of isoproterenol (1 μg/min). *Bottom*, isometric time-tension relationship evaluated as a function of right ventricular end-diastolic pressure. Points are simultaneous with those used for calculation of right ventricular stroke work relationship shown above. (From Siegel et al., with permission of the publisher.)

lenging and important applications of new techniques for determining the contractile state of the intact heart.

The Current Status of the Evaluation of Myocardial Function in the Critically Ill

Measures of integrated myocardial capabilities including both myocardial and pump functions have been obtained from studies of left ventricular ejection and mean ejection rate and from the relationship between ejected and residual ventricular volumes. These relationships, as well as the evaluation of the range of ventricular function calculated by the classic Starling-Sarnoff relationship between ventricular stroke work and filling pressure, have been useful in determining a general range of overall cardiac function. While this kind of analysis cannot separate out the quantitative contribution of intrinsic myocardial factors, as distinguished from factors influencing ventricular volume and the effects of alterations in afterload, ventricular function relationships at least have the advantage of being easily obtained at the bedside of the critically-ill patient. Ventricular function relations can provide information concerning the relative level of cardiac function and permit alterations to be evaluated in an individual patient as a function of time and changing clinical condition. That this type of information does provide a useful clinical guide when evaluated in the light of a sophisticated understanding of myocardial force-velocity relationships is demonstrated by a variety of studies of patients who had acute illnesses where cardiovascular hemodynamics were evaluated as a guide to therapy. The interrelationship between the depression in myocardial work-filling pressure relationship expressed by ventricular function and the true depression in myocardial contractility reflected by alteration in durational aspects of the isometric-time-tension relations is illustrated in figure 18. The patient was in hyperdynamic septic shock. She was hypotensive at a time when the cardiac index was in excess of 4 l/min/m². Right ventricular stroke work was correlated with right ventricular end-diastolic pressure and with simultaneously-determined changes in time from onset of contraction to maximum dp/dt (Δt dp/dt). As has been shown, this index is inversely proportionate to myocardial contractility as quantified either by the isometric time-tension index or by direct determination of the maximum velocity of isotonic shortening (Vmax), in that the longer the interval Δt dp/dt, the lower the contractility. In this patient, right ventricular stroke work was approximately 26 gm meters and was performed at an end-diastolic pressure of 19 mm Hg. The simultaneously-determined Δt dp/dt was 65 msec, which, in view of the patient's high heart rate of 110 per minute, represented decreased myocardial contractility when compared with values for patients not in shock. That a significant increase in contractility over the baseline was possible was revealed by the administration of isoproterenol (1 μg/min), which increases myocardial contractility both in nor-
normal patients. Right ventricular stroke work increased slightly to 29 gm meters, but this was performed at a right ventricular end-diastolic pressure of 11 mm Hg, representing a significant shift to an improved ventricular function curve. The infusion of isoproterenol also resulted in a progressive decrease in the Δt dp/dt relationship to 60 msec after 16 minutes and to 55 msec after 41 minutes, without significant increase in heart rate. These determinations demonstrate not only that significant levels of myocardial depression and decreased contractility can occur in the presence of an increased cardiac output in some critical illnesses, but also that serial monitoring of even a few points from the ventricular function relationship can provide some measure of the effectiveness of a therapeutic program designed to improve the myocardial contractile state.

**HYPOVOLIC NONSEPTIC SHOCK**

A considerable amount of pertinent information concerning myocardial function can also be obtained by examination of a crude ventricular function relationship in which left ventricular stroke work is plotted against the central venous (mean right atrial) pressure.

Although this type of analysis assumes no major disparity between the functions of the two ventricles, such that the central venous pressure does not reflect alterations in the left ventricular end-diastolic pressure, this assumption based on "lumped" physiologic parameters has appeared to be reasonably valid if patients with pulmonary embolus shock or myocardial infarction shock are excluded. A more important consideration for patient care is that this information can be obtained readily by the current techniques of bedside catheterization and is available to the interested physician at the patient's bedside, in the operating room, or at any other location where the critically-ill patient happens to be treated. An example of these interrelations in patients in clinical shock is given in figure 19. The values for a group of elderly normal patients appeared to lie in a generally good range of this crude ventricular-function relationship, in that the amounts of stroke work performed by their left ventricles were carried out at relatively low central venous pressures. However, most patients whose shock processes were on

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**Fig. 19. Ventricular function relationships in shock.** Log-log plot of left ventricular stroke work in gm meters on the ordinate, vs. central venous pressure in mm Hg on the abscissa. (From Siegel et al., with permission of the publisher.)

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a hypovolemic basis, due either to loss of blood or to reduction in circulating intravascular volume, had fair or poor ventricular function relationships.

Septic Shock

Examination of this relationship in patients whose shock process was due to sepsis (Fig. 19), however, disclosed a rather clear-cut separation between those patients whose septic condition was characterized by low cardiac output, or hypodynamic septic shock, and those who manifested a hyperdynamic syndrome with increased cardiac output. The patients who had a hypodynamic septic shock process, without exception, had poor ventricular function, whereas those with hyperdynamic septic shock fell into a fair or good range. Only patients in normodynamic septic shock with normal levels of cardiac index appeared to be distributed between the fair and good ranges rather evenly; this group of patients appeared to be in less severe septic shock. These data suggest that cardiac function is usually depressed in patients in septic shock, but that the degree of depression is less in patients manifesting the hyperdynamic septic shock syndrome than in those with hypodynamic septic shock.

In contrast to patients with non-septic hypovolemic shock, where vascular tone is increased over normal, all patients with septic shock have vascular tone relationships which are decreased from normal. This decrease in the pressure-flow relationship of peripheral vascular beds is characteristic of the septic process and is independent of the level of cardiac output. Septic patients also have severely abnormal oxygen consumption. With this defect in oxygen consumption both the absolute level of oxygen consumption and the ratio of ml of oxygen extracted per l of total blood flow (effective oxygen transport ratio) are reduced.

The demonstration of greater reduction in ventricular function in septic-shock patients manifesting low-cardiac-output syndrome is of great interest since the degree of abnormality in this effective oxygen transport ratio (EOT)
appears to be directly related to the level of cardiac output and, therefore, is influenced by the level of ventricular function, and presumably by the effectiveness of the myocardial contractile state.177

**Hepatic Cirrhosis with Portal Hypertension**

A similar analysis of this crude ventricular function relationship in patients with degenerative hepatic disease presenting with portal hypertension secondary to hepatic cirrhosis (fig. 20) also reveals a significant relationship between the level of myocardial function and the degree of abnormality in cardiac output.22,175 Cirrhotic patients with a hyperdynamic cardiovascular state appear to have better ventricular function than cirrhotic patients with normal or decreased cardiac outputs, although this segregation was not as clean as that seen in septic shock patients.177 Of even greater interest, however, was the fact that 16 of the 19 postoperative deaths in the patients shown in figure 20 occurred in individuals whose preoperative crude ventricular function relationships were either fair or poor. This was even more striking when the patients who were operated on an emergent basis were considered as a separate group. Seven of 12 of these patients had poor ventricular function relationships preoperatively, and four were actually in overt myocardial failure. Eleven of the 12 emergent patients died; the only survival was the one patient whose preoperative ventricular function relationship was rated good. Patients with extensive cirrhotic disease, like the septic-shock patients, also manifest marked abnormalities in vascular tone relationships, in that they have reduced peripheral resistance at any given level of cardiac output when compared with normal patients or with patients in non-septic shock.175

These patients also have abnormalities in oxygen consumption similar to those found in septic-shock patients.175 In order to better understand which interrelationship between myo-

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**Fig. 21.** Relative peripheral shunting in cirrhosis and portal hypertension. Log-log plot of effective oxygen transport in ml O2/l blood flow vs. total peripheral resistance in dyne-sec-cm^-5. Points are plotted with regard to previously-defined means for patients in states of non-septic and hyperdynamic septic shock and patients who were not in shock and had no known hepatic disease. (From Siegel *et al.*,175 with permission of the publisher.)
cardial and peripheral factors has a major influence on the response to anesthesia and surgery in the cirrhotic, it has been useful to consider the relationship between the effective oxygen transport ratio and total peripheral resistance (fig. 21). This function, designated "relative peripheral shunting" (RPS), reveals that in cirrhosis, as in septic shock, a marked increased cardiac output is associated with inefficient oxygen extraction.172,182 There is a separation of patients with the high cardiac output syndrome, "hyperdynamic" liver disease, from the other groups studied. In the hyperdynamic group, the level of oxygen extraction is reduced as a function of the decreased peripheral vascular resistance when compared with the mean value for normal patients. The value of the RPS relation for the hyperdynamic cirrhotic patient lies on the opposite side of the normal mean from the values found in patients with non-septic shock. The quantitative degree of the relative peripheral shunting abnormality in the hyperdynamic cirrhotic patient was comparable to that found in patients in hyperdynamic septic shock. Since vascular tone was decreased in every patient with severe hepatic disease, regardless of the level of cardiac output, in severe hepatic disease, as in severe sepsis, there may be anatomic or functional arteriovenous shunts, in which shunt flow is a direct function of total aortic flow. This finding also suggests that, in contrast to normal shunting over which some degree of sympathetic control exists, there is a relative paralysis of regulatory control over these pathologic shunts, so that the degree of arteriovenous shunting is a passive consequence of the increase in flow, which is influenced in turn by the adequacy of the myocardial contractile state. In this condition, as

![Diagram](image_url)

**RELATIVE PERIPHERAL SHUNTING**

**VENTRICULAR FUNCTION**

**LEFT VENTRICULAR STROKE WORK**

**CENTRAL VENOUS PRESSURE (mmHg)**

### Function Index:

\[ \theta = -\arctan \left( \frac{\ln(Y) - \ln(X)}{\ln(Y) - \ln(X)} \right) \]

Where \( \theta = 0.17 \) and \( \varphi = 1.10 \)

\[ X = TPR \]
\[ Y = EOT \]
\[ \gamma_{HSS} = 0.678 \times 0.1690 \]
\[ \gamma_{HSS} = 0.203 \times 0.9609 \]

**Function Index:**

\[ \theta = \arctan \left( \frac{\ln(Y)}{\ln(X)} \right) \]

\[ X = CVP \]
\[ Y = SW \]
\[ \gamma_{G-F} = x^{1.226} \]
\[ \gamma_{F-P} = x^{0.745} \]

**Fig. 22.** Derivation of computer-based indices of relative peripheral shunting (RPS) and ventricular function (VF). (From Siegel and Williams,182 with permission of the publisher.)

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in septic shock, patients who have a great deal of peripheral and pulmonary shunting need better ventricular function relations to survive.175

Like decreases in the crude ventricular function relation in the cirrhotic, abnormalities in relative peripheral shunting have grave prognostic significance. Among patients in whom oxygen transport was determined preoperatively, all elective surgical candidates who died had the greatest degrees of abnormality in effective oxygen transport and peripheral resistance. In this respect seven of the ten elective surgical candidates in figure 21, whose effective oxygen transport values (EOT) were less than 20 ml/1 total blood flow and whose total peripheral resistances (TPR) were less than 1,500 dynes-sec-cm\(^{-5}\), died following portal decompression.

At any given level of myocardial contractility the exact nature of the heart’s operation on the unique length–tension and force–velocity relationships characterized by a given \( V_{\text{max}} \) is determined by extracardiac factors which influence diastolic filling and afterload. It seems apparent, therefore, that the prognosis of a given patient should be greatly influenced by the nature of the interaction of central and peripheral cardiovascular factors. The application of computer techniques has permitted the evaluation of the interdependence of these variables to be quantified as functions of one another, so that they can be used as sophisticated indicators of the patient’s overall condition.174,175,182 As shown in figure 22, using the previously-defined mean values for the major clinical groups of patients in shock in the relative peripheral shunting function, as well as lines of separation between good, fair, and poor ventricular function, it is possible to locate the individual values for any patient and to characterize these by a number which quantitatively describes his position in a two-dimensional space.182 Studies of this sort in patients with cirrhosis and portal hypertension have shown that a survival index which expresses the statistical probability of an individual patient’s surviving portal decompressive surgery can be computed. As shown in figure 23, evaluation of the normalized index of crude ventricular function (VF) reveals that in order for an individual patient to survive the stress of a major portal decompressive procedure in the presence of severe hepatic disease, an increasing level of peripheral abnormality (RPS index) must be balanced by a concomitant increase in the net myocardial function, as expressed by the crude ventricular function relationship. In the 44 patients studied prior to portal venous decompression, there were no operative deaths among the 17 patients whose values fell in the “good” range, with normalized survival indexes at values greater than zero. A second line of separation could be established, creating a “fair” range in which approximately 50 per cent of the patients operated upon survived decompressive surgery, with normalized survival indexes from zero to −50. Finally, a “poor” range could be identified, in which the probability of survival was 20 per cent or less, normalized survival indexes less than −50. The use of these computer-based assessment techniques can provide the surgeon or anesthesiologist with a quantitative index of circulatory function which can be followed over time as a guide to changing clinical conditions.174,182 A similar relation of a normalized prognostic index to the risk of surgery has been found in preoperative studies of elderly patients.174 While it is clear that all that

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**Fig. 23.** Derivation of computer-based survival index for the prediction of operative mortality in cirrhosis and portal hypertension. (From Siegel and Williams,182 with permission of the publisher.)
this type of analysis can do is to designate ranges of statistical probability, the directional change in these normalized indices of cardiovascular function over time in an individual patient can be of use in evaluating the effectiveness of therapy.

**Myocardial Infarction Shock**

The interaction between myocardial function and abnormalities in peripheral vascular tone appears to be important in other disease entities as well. The studies of Gunnar 91, 92 and others 117, 120, 125 have shown that a significant number of patients with myocardial infarction shock have normal or decreased peripheral vascular resistance. Although no explanation for the inappropriate vasomotor activity has been proven clinically, experimental studies suggest the possibility of reflex inhibition arising in the occluded coronary arteries,12, 36 or from left ventricular stretch receptors.26, 124 Gunnar's studies also suggest that a vasodilator agent (isoproterenol) which further reduces vascular tone, even though it has a positive inotropic effect in some patients, may indeed worsen the overall ventricular function in myocardial infarction shock.22 This may be due to a further reduction in coronary flow because the rigid coronary arteries produced by atherosclerotic occlusive disease may be unable to undergo active vasodilation. This might result in a net decrease in oxygenation to the remaining myocardium which could more than outweigh the Vmax changes produced by the inotropic action of the catecholamine.

In these patients, use of a positive inotropic agent with vasoconstrictor properties improves chances of survival.11, 91-93 These observations, which suggest that an inotropic vasoconstrictor agent is appropriate for treatment of patients with myocardial infarction shock, are interesting in view of other studies 62, 62, 99 which have demonstrated that patients who are not in shock but have primary myocardial disease secondary to diffuse coronary artery disease, myocardiopathies, or ventricular hypertrophy secondary to valvular lesions are benefitted by the use of isoproterenol.

These studies of primary cardiac disease, and studies of various other forms of shock 4, 50, 100, 121, 170, 200, 228 and hepatic cirrhosis associated with portal hypertension 172 have shown unequivocally that the physician must determine which pathophyslogic pattern he is dealing with in order to choose the proper inotropic agent. In addition, he must have quantitative information concerning the individual patient's response pattern to decide the proper moment to intervene with vasoactive drugs. Even more important, the physician must be able to quantify the patient's response to anesthesia during surgery, since the quantitative response to a given agent and the ratio between the effective and the toxic dose vary from one individual to another.

**Determining the Response to Anesthesia and Surgery in an Individual Patient**

Data obtained from bedside catheterization and the immediate processing of this information by appropriate computer techniques 176, 174, 182 are essential to the best management of the critically ill, since it is the specific pattern of abnormalities occurring in an individual patient at a given moment which determines his course in the next segment of time. Using information of this sort it has been possible to improve preoperative, intraoperative, and postoperative management of high-risk patients and probably to avoid serious complications.99, 174, 175, 176

The equipment necessary for evaluation of a critically-ill patient (Fig. 24) consists of a physiologic recorder with a direct readout of the photographic type. The recorder is contained in a portable shock cart with its own power supply. It has two electronic amplifiers capable of recording intravascular pressures using mechanoelectric strain gauges. It has an electrocardiograph amplifier and an amplifier capable of accepting the input from a photoelectric densitometer for recording the indocyanine-green dye dilution curve, from which the calculation of cardiac output may be determined. This cart has a working surface at a convenient height which also provides a place for the constant-withdrawal syringe used for the dye dilution curve, and it has positioning arms for the support of the strain gauges and the densitometer cuvette. Figure 24 also shows the relatively inexpen-
sive portable Olivetti Programma 101 computer with its magnetic program cards on which the primary data can be analyzed immediately. It is also necessary to have laboratory facilities for immediate and accurate blood gas determinations.

The cardinal point is that the entire system, both physiologic recorder and computer, can be brought to the patient’s bedside, or to the operating room, and the data can be analyzed and the therapeutic decisions made by the physician, surgeon, or anesthesiologist in charge of the critically-ill patient. The simplicity of the computer and its ease of use have obviated the major obstacle to the use of physiologic determinations in seriously-ill patients, the difficulty and time involved in the computation of cardiac output and other physiologic correlates using the data obtained from the physiologic recorder. These computed data, normalized in such a way as to be related to mean values for groups of patients in various shock states previously studied, are then plotted on a standard form, and any drug interventions or operations indicated. It enables the physician caring for the patient to see a continuous time-based function showing not only the changes in blood pressure and cardiac index but also the directional changes in the various significant cardiovascular functions. It also permits him to reference the physiologic pattern present in his patient at any given time to the previous experience with regard to patients in septic or non-septic shock.

An example of a clinical time history is shown in figure 25; the course of a patient is plotted against time with respect to alterations in cardiac index, blood pressure, and computer-based indices of vascular tone (VT), effective oxygen transport (EOT), relative peripheral shunting (RPS) and ventricular function (VF), normalized with regard to mean values for groups of patients in various previously-studied shock states. In addition, the computer-based
survival index which relates the alterations in ventricular function to the peripheral vascular indices is shown.

Using these data, serial determinations of response to therapy can assist the physician in determining the effectiveness of a given course of action. Figure 25 illustrates the use of online cardiovascular evaluations in delineating the response of an individual elderly patient to anesthesia and elective surgery. This patient, a 70-year-old hypertensive woman, underwent elective cholecystectomy for cholelithiasis. Preoperatively, the patient was felt to represent a high risk because of a long history of systemic hypertension with marked left ventricular hypertrophy, and because of previous episodes of congestive cardiac failure compensated for by chronic treatment with digitalis. Preoperative determination of the correlated cardiovascular functions revealed a good range of ventricular function but showed an increased vascular tone relationship, probably due to the hypertensive disease; this impression was supported by demonstration that the index of relative peripheral shunting showed a pattern compatible with mild vasoconstriction, lying between the normal and non-septic shock means. The patient's survival
index showed her to be a relatively good risk, in a range associated with a statistical probability of survival of 90 per cent or better. Her response to oxygen demonstrated a further increase in the level of ventricular function relationship and a directional improvement in survival index. Of special significance in this patient, however, was the fact that with thiopental induction there was a decrease in the ventricular function index, although alterations in cardiac index and blood pressure were negligible. The dose used was not excessive, but this is compatible with observations in animals that when borderline cardiac compensation exists, relatively severe myocardial depression can be brought about by small doses of barbiturates. Intubation and initiation of surgery under nitrous oxide and oxygen anesthesia produced a slight improvement in the ventricular function index from poor to fair. There was a further increase in the vascular tone relationship to a level of vasoconstriction somewhat higher than the mean value for non-septic shock patients, as well as a reduction in the general level of the relative peripheral shunting index. This may reflect both better oxygenation and the stimulation of the trauma of intubation and skin incision. The important fact is that the surgeons monitoring this patient were alerted to the possibility of further deleterious changes, even though there was no significant alteration in blood pressure or cardiac index. When halothane anesthesia was begun, the patient had a profound myocardial depression compatible with the known force-velocity changes described for this drug.257 This probable decrease in myocardial contractility was reflected by a fall in the ventricular function index into the poor range. However, there was only a slight narrowing in the pulse pressure and only a minimal change in mean blood pressure. The vascular tone and relative peripheral shunting indices decreased somewhat, but determinations of the survival index clearly showed that the patient's prognosis had changed materially, and that this change was due primarily to a deterioration of ventricular function relationships, causing a fall in cardiac output. The ordinary determinations of blood pressure failed to indicate the degree of depression in myocardial function or the magnitude of the fall in cardiac output. There was no major blood loss during the procedure, and the estimated volume deficit was completely replaced; nevertheless, the patient also had a decrease in the index of relative peripheral shunting, caused by an increase in effective oxygen transport occurring at a very high vascular resistance. This finding is similar to that seen in patients with severe non-septic shock.177 It supports the contention that the major cause of increased vascular tone was a reflex response due to the low flow,174, 160, 161, 218 brought about by a primary myocardial depression, so that nearly all the total systemic blood flow was being directed to metabolizing capillary beds, with very few functioning arteriovenous connections. This demonstration of severe myocardial depression precipitated the termination of the halothane anesthesia, and the patient's anesthetic program was changed back to nitrous oxide and oxygen. This was followed by an improvement in ventricular function relationship and a return of her survival index to the "good" range, where the statistical probability of survival appears to be 90 per cent or greater. During the 12 hours following surgery and termination of anesthesia, the patient's ventricular function index gradually returned towards the "good" range and the cardiac index neared control level. Postoperatively the patient's blood pressure was not only lower than the preoperatively, but was lower than any value obtained during surgery itself. Also, during the postoperative period, vascular tone index decreased toward normal and the ventricular function index during the first postoperative day showed an overshoot. This overshoot appears characteristic of patients who do well following major surgery; its absence is associated with a poor prognosis unless beneficial positive inotropic measures can be effected.174, 152

This case illustrates the effect of an episode of acute myocardial depression induced during anesthesia, and also the marked degree of physiologic compensation possible through the actions of the various vasoconstrictor mechanisms which result in an increase in vascular tone. However, maintenance of blood pressure by increasing peripheral resistance may
cause further myocardial depression in the heart working at the limits of its compensation. Although many poor-risk patients tolerate halothane or other negative inotropic anesthetic agents well, the availability of on-line determinations enabled immediate recognition of myocardial depression in this individual before a significant drop in blood pressure had occurred, and made possible an intelligent decision to terminate administration of one anesthetic drug and substitute another with less myocardial depressant effect. Probably a major intraoperative catastrophe was averted by early recognition of occult myocardial failure and its reversal before irreparable damage occurred.

Serial observations of integrated cardiovascular functions appear to enable better control of preoperative hydration and blood replacement in elderly and poor-risk patients. Bedside cardiovascular evaluation also provides a more rational guide to the use of digitals preparations and other inotropic agents in the management of impending, or overt, hemodynamic failure in the pre- and postoperative periods, especially in patients whose postoperative courses are complicated by hyperdynamic hepatic failure or sepsis. In the cardiac arrest patient they can indicate the efficacy of closed-chest massage and can identify pulmonary emboli which require operative intervention. Our current studies in high-risk general surgical patients suggest that there is less further intraoperative myocardial depression in patients with borderline ventricular function relationships when Innovar or nitrous oxide is used in preference to halothane anesthesia; however, there is considerable individual variation.

Conclusion

The basic mechanics of myocardial contraction have been outlined and the alterations induced in the contractile state by myocardial failure and by various positive and negative inotropic agents discussed. The interactions between the level of integrated myocardial status and the state of peripheral vascular response in different disease states indicate that therapeutic programs must be carefully considered in light of specific disease processes.

While most studies of the cardiovascular system suggest that diethyl ether, cyclopropane, nitrous oxide, or Innovar, which appear to have only minor net myocardial depressant effects, should offer greater protection to the high-risk patient than agents with more pronounced negative inotropic effects, it is also clear that these conclusions represent generalities which must be confirmed in every critically ill patient. The numerous interacting variables which condition the individual’s response at any given moment make it imperative that the important decisions in each case be controlled by quantitative data which adequately describe the patient’s unique temporal cardiovascular status. This reviewer believes that the overall operative mortality rate in the high-risk patient will be improved significantly only when detailed serial measurements of relevant cardiovascular physiologic correlates are carried out after each alteration in drug or anesthetic dosage, during all important surgical maneuvers and throughout the immediate postoperative period. This can be managed by any interested and well-trained professional, and the knowledge obtained will permit the surgeon and the anesthesiologist together to tailor their therapy to suit the patient’s needs.

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